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Authors: Elisa Bruno, Giulia Maira, Andrea Biondi, Mark P Richardson, on behalf of the RADAR-CNS Consortium

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Ictal hypoxemia: a systematic review and meta-analysis

Elisa Bruno[a,b], Giulia Maira[a,c], Andrea Biondi[a,b], Mark P Richardson[a,b], on behalf of the RADAR-CNS Consortium[b]

[a] Institute of Psychiatry, Psychology & Neuroscience, Division of Neuroscience, King's College London, UK

[b] www.radar-cns.org

[c]Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Section of Neurosciences, University of Catania, Catania, Italy

Corresponding author

Professor Mark P Richardson

Institute of Psychiatry, Psychology & Neuroscience

Division of Neuroscience

King's College London

Maurice Wohl Clinical Neuroscience Institute

Ground Floor (G.39), 5 Cutcombe Road, Camberwell, London, SE5 9RX

Tel: (+44) 20 7848 5429

mark.richardson@kcl.ac.uk

Highlights

- Ictal hypoxemia is frequent in adults and in patients with tonic-clonic seizures
- Only 20% of seizures presents with desaturations below 85%
- The severity of hypoxemia is a major clinical concern
- Seizures with desaturation have a longer duration

Abstract

Purpose: To estimate the incidence of ictal hypoxemia (IH) and to identify clinical and study-related factors modulating the estimate.

Methods: We searched articles recording concurrent peri-ictal and ictal EEG and Sp02 in adults and children with epilepsy. Studies reporting the total number of seizures recorded and the number of seizures with IH were included in a random-effects meta-analysis. A random-effects meta-regression was used to identify variables affecting study heterogeneity.

Results: Twenty-one studies, including 917 participants and 1,840 with SpO2 data available were included. The meta-analysis showed a pooled incidence of IH of 35/100 seizures (95% CI 27-44). Sp02 desaturation threshold was associated with the incidence of IH, with less severe desaturations resulting in higher IH frequencies. The incidence of IH was 41/100 seizures (95% CI 29-54) for adults

and 47/100 seizures (95% CI 15-78) for tonic-clonic seizures. The meta-regression showed that SpO2 desaturation severity was the sole variable significantly correlated with the incidence of ictal hypoxemia (p=0.00).

Conclusion: In a population with refractory epilepsy IH is a frequent phenomenon, especially in adults and in patients presenting with tonic-clonic seizures. The severity of IH appeared independent from the age group and from seizure type and is probably the major clinical concern for its correlation with potentially life-threatening cardiorespiratory alterations and sudden unexpected death in epilepsy (SUDEP).

Introduction

Ictal respiratory changes (IRCs) have been recognized for more than 100 years [1] and are commonly seen in generalized and focal seizures [2]. IRCs include a range of alterations, from central and obstructive apnea, tachypnoea, bradypnea to hypoventilation and hypoxemia [3]. IRCs, and most importantly respiratory depression such as hypoxemia, hypercapnia and central apnea, have attracted attention in several clinical contexts, including SUDEP [4-6] and seizure detection in the epilepsy monitoring unit [7-9].

SUDEP is the most common cause of death directly related to epilepsy [10]. Although the exact pathophysiology of SUDEP remains unclear, most witnessed cases are associated with early postictal tachypnoea, hypoxemia and terminal apnea, following a generalized convulsive seizure and preceding cardiac arrest [11,12]. Moreover, the combination of ictal hypoxemia (IH, defined as a drop in peripheral capillary oxygen saturation (SpO2) below 92% during a seizure) and apnea appears a stronger predictor of risk of SUDEP [13], while the duration of IH seems to correlate with other SUDEP risk factors, such as postictal immobility [14]. In addition, cardiac repolarization abnormalities, which have been associated with potentially life-threatening arrhythmias and may also play a role in the pathophysiology of SUDEP [15], are more likely to occur in seizures associated with IH, and their severity is correlated with the duration and severity of IH [16]. Due to its clinical importance, IH has been extensively studied and demonstrated in approximately one-third of generalized and focal seizures [13,17,18]. However, the rate and severity of IRCs and IH in patients with epilepsy varies considerably across studies. This variance likely reflects differences in demographic and clinical variables, seizure localization, as well as polytherapy with antiepileptic drugs (AEDs) [19]. In addition, methodological issues can also be responsible for the mixed findings, including methods used to assess and define hypoxemia.

Understanding the distribution of IH and the influence of clinical factors on its occurrence, severity, duration and association with apnea may help at identifying populations at higher risk of SUDEP who might benefit from the use of SpO2 and hypoxemia-triggered intervention to reduce such risk.
We aimed to perform a systematic review of the literature and meta-analysis to estimate the incidence of IH and to identify clinical and study-related factors modulating this phenomenon.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Handbook guidelines [20,21]

Criteria for considering studies for this review

Retrospective and prospective studies (case-control, cohort or case series) recording concurrent peri-ictal and ictal EEG and Sp02 in adults and children with epilepsy were considered for inclusion. Studies focusing on neonatal seizures only were excluded. Criteria and SpO2 cut off used to define hypoxemia were extracted and considered as separate variables in the meta-regression, as potential sources of between studies heterogeneity.

Search methods for identification of studies

A systematic search with no language restrictions was carried-out to identify all relevant published and unpublished studies. The search strategy included the terms “epilepsy”, “seizure”, “hypoxemia” and “oxygen saturation” and is reported in Appendix S1 (Supplementary information). The search was conducted from the first date available (1958) up to May 30, 2018 in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategies for each database were based on the strategy developed for MEDLINE, taking into account the differences in controlled vocabulary and syntax rules. In addition to the electronic searches, we hand-searched reference lists of all available review articles and primary studies and hand-searched the references quoted in the most recent congress proceedings (e.g. International Epilepsy Congress, European Congress on Epileptology).

Data collection and analysis

Two review authors (GM and AB) independently assessed the titles and abstracts of all the studies identified by the electronic searching or hand-searching. Full texts of potentially relevant studies were obtained and screened. We resolved any disagreements concerning study inclusion and exclusion by discussion. For each study included, two review authors (GM and AB) independently extracted the following data on an ad-hoc created data collection form: study design (prospective, retrospective) and setting (inpatients, outpatients); demographic and clinical data of the population (number of patients, age group, gender, type of epilepsy, drug-resistance, AEDs

administration/withdrawal during the recording); number of seizures recorded, seizure type (tonic-clonic versus non-tonic-clonic) and focus (including focus side), definition of seizure onset (EEG, clinical, either EEG or clinical); EEG characteristics: type (scalp, intracranial), number of electrodes used (standard, non-standard), duration (continuous, intermittent, number of hours recorded), use of video recording; definition of hypoxemia; number of seizures presenting with IH; mean ictal SpO2, mean SpO2 nadir; time of SpO2 nadir; mean duration of IH.

Quality assessment

The quality of included studies was evaluated using a standard assessment tool, that was re-adapted (Appendix S2, Supplementary material), and included sample representativeness, condition assessment, and statistical methods [22]. Each study was given a quality score of 0 to 8 based on fulfilment of the quality criteria. The quality score was considered as a separate variable in the meta-regression for studies included in the meta-analysis.

Data synthesis and analysis

Studies reporting the total number of seizures recorded and the number of seizures with IH (including 0), were included in a meta-analysis.

In addition, meta-analysis was separately fitted according to IH severity (SpO2<92%, SpO2<90%, SpO2<85%, SpO2<80%, SpO2<70%, SpO2<60%), seizure type (tonic-clonic versus non-tonic-clonic) and age group (adults versus children), when these variables were specified by an adequate number of studies. We used the 'metaprop_one' command in Stata 14.0 to estimate crude incidence rates along with their 95% confidence intervals (CI) and we expressed the estimates as the number of seizures with IH per 100 seizures. We reported the pooled, weighted estimate generated by random-effects models. To handle the studies with zero events, we used Freeman–Tukey double arcsine transformation which stabilizes the variance of the proportion restricting the 95% CI within the range of 0 and 1, even in the presence of zero events [23]. As a sensitivity analysis, the pooling process was repeated after the successive removal of incidence studies with a low-quality score. The I^2 was used to quantify the magnitude of between-study heterogeneity and the Cochrane Q statistic was calculated to determine significance. Publication bias was investigated statistically using Begg's and Egger's tests. To determine the influence of the clinical variables and of the study-level factors on the observed variability, we used random-effects meta-regression. We regressed one variable at a time. Significance level was established at $p<0.05$. All analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, U.S.A.).

Results

Study selection and quality assessment

The search of electronic databases yielded 1,344 references (Figure 1). Four additional studies were identified by hand-searching. After duplicates and non-relevant studies were removed, the titles and abstracts of the remaining studies were reviewed and the full-text of 42 articles with potentially relevant studies was assessed. Eight papers were excluded after contacting the corresponding authors as the populations were overlapping [15-17, 24-26, 40, 48]. Finally, 21 published studies were considered eligible for this review and their characteristics are summarized in Table 1. Of the 21 studies, seven studies [14, 27-32] were considered for the qualitative synthesis only as they reported the occurrence of IH without specifying its frequency. The remaining 14 studies [4-6, 8, 9, 13, 18, 33-39] were included in the meta-analysis. Quality assessment revealed a median study quality score of 6/8 (range 1-8) and yielded higher scores (7/8) for those studies included in the meta-analysis.

Summary of characteristics of the studies

Twenty-one studies, enrolling 917 people living with epilepsy (43.7% female; 45.3% male; 11.0% not reported) and a total of 2,599 seizures, 1,840 with SpO2 data available. Fourteen included adults, four children only, two both adults and children, one did not report participants' age.

Six studies included people with different focal epilepsy types [5, 13, 30, 31, 34, 38], two with TLE only [37, 39], 11 included a combined sample of focal and generalized epilepsy [4, 6, 13, 14, 18, 28-30, 33, 35, 36] and two did not report the epilepsy type [8, 25].

Five studies included focal seizures only [5, 31, 37-39], 14 included both focal and generalized seizures [4, 6, 9, 13, 14, 18, 28-30, 32-36] and two did not report the seizures type [8, 25].

Three studies included drug-resistant patients [8, 37, 38], two both drug-resistant and non-drug-resistant patients [13, 18] and 16 did not specify if patients were drug-resistant or not [4-6, 9, 14, 27-36, 39].

All the studies used scalp EEG, with three studies including also intracranial EEG [9, 30, 36]. The majority of the studies were based on continuous EEG recording, using a standard 10-20 system and video recording; only two studies used less electrodes than standard [5, 27]. Oxygen desaturation was assessed through pulse-oximeter in all the studies.

The mean seizure duration was 95.6±30.5 seconds (range 39.0-137.0) in ten studies [5, 14, 18, 29, 31, 33-37] and 122.3±45.2 seconds (range 86.0-173.0) for seizures with desaturation [18, 36, 37].

The mean baseline SpO2 was 97.5±0.5% (range 97.0-98.0) in three studies [14, 32, 34]. The mean time to SpO2 nadir was 47.0±24.3 seconds (range 31.0-75.0) in three studies [4, 5, 37], and the mean SpO2 nadir was 82.5±6.5% (range 74.0-88.9) in seven studies [5, 8, 14, 28, 34, 35, 37] and <60.0% in two studies [13, 18].

The mean IH duration was 96.8±23.3 seconds (range 73.1-130.0) in five studies [5, 14, 29, 34, 37] with a mean SpO2 desaturation of 84.6±9.8% (range 71.0-93.1) reported in four studies [4, 31, 32, 38].

Two studies [14, 29] and two additional studies [17, 40] which was only included for this variable only [34] reported the occurrence of ictal hypercapnia with a mean end-tidal CO_2 ($ETCO_2$) elevation from baseline of 19.1± 12.6 mmHg. Four studies [4, 8, 31, 36] reported that in 70 of 213 seizures with IH (32.8%) was associated with central apnea.

Meta-analysis

The pooled incidence of IH for the 14 studies included in the meta-analysis [4-6, 8, 9, 13, 18, 33-39] was 35/100 seizures (95% CI 27-44) (Figure 2), with a significant between study heterogeneity (I^2= 92.9%, Q p-value=0.000). Egger's and Begg's test were not significant (p= 0.2) indicating a low risk of publication bias. Sp02 desaturation threshold was associated with the incidence of IH, with less severe desaturations resulting in higher IH frequencies (Figure 3 A). The majority of studies (8/14) defined ictal hypoxemia as an SpO2<90%, giving an incidence of IH of 33/100 seizures (95% CI 18-47).

Studies including adults presented with an incidence rate of 41/100 seizures (95% CI 29-54) while the incidence was 31/100 seizures (95% CI 19-42) for studies including children only (Figure S1, Supplementary material).

Six studies reported the incidence of IH separately for tonic-clonic and non-tonic-clonic seizures. The analysis performed on these studies (Figure 4A and 4B) showed an IH incidence of 47/100 seizures (95% CI 15-78) for tonic-clonic and of 32/100 seizures (95% CI 12-55) for non-tonic-clonic seizures.

The meta-regression (Table 2) showed that SpO2 desaturation severity was the sole variable significantly correlated with the incidence of ictal hypoxemia (p=0.00) (Figure 3B), and accounted for 40.03% of the observed between study heterogeneity. No other clinical or methodological variables were associated with the estimates, including seizure and epilepsy type.

All the studies included in the meta-analysis were judged at high quality and the planned sensitivity analysis was not performed.

Discussion

This systematic review and meta-analysis indicated that IH is a frequent and self-limiting feature of both focal and generalized seizures. We found that in patients undergoing EEG-telemetry more than one third of seizures are associated with IH, with a pooled frequency of 35% (95%CI 27-44). Higher estimates were found for tonic-clonic seizures (47%, 95% CI 15-78) and in seizures occurring in adult

populations (41%, 95% CI 29-54). Conversely severe IH was a rarer phenomenon and only 22% (95% CI 13-32) of seizures presented with ictal oxygen desaturations below 85%.

In all the studies identified, IH measures were based on digital pulse oximetry, which estimates systemic hypoxemia and constitutes an indirect measure of cerebral oxygenation. However, whether the identified SpO2 desaturations are related to centrally mediated hypoventilation and cerebral hypoxemia or conversely to seizure-associated peripheral vasoconstriction, is uncertain. A more precise indicator of primary respiratory disturbances is represented by the simultaneous use of ETCO2 measurement (and index of hypoventilation) and its association with IH supports the presence of a primary respiratory inhibition. However, a concomitant measurement of SpO2 and ETCO2 was reported in four studies only [14, 17, 29, 40] and none of them was included in the meta-analysis. Four additional studies [4, 8, 31, 36], three of which included in the meta-analysis, also reported that IH was accompanied by central apnea in 32.8% of the seizures recorded, supporting a centrally mediated ventilatory dysfunction.

The higher frequency of IH in tonic-clonic seizures is an interesting clinical finding and may be related to the ictal modulation of the respiratory centres. Although the mechanisms supporting respiratory changes during seizures are still largely unknown, the brainstem respiratory centres appear to be mainly regulated by descending ipsilateral limbic pathways [19, 41]. The simultaneous involvement of both the hemispheres and descending circuits during convulsive seizures may more likely lead to more frequent and severe IH. However, additional peripheral mechanisms of hypoxemia, including significant muscle activation and airway obstruction, cannot be excluded.

The meta-analysis additionally showed a higher incidence of seizure with IH in studies focused on adults (41%, 95% CI 29-54) as compared with those enrolling children only (31%, 95% CI 19-42). These findings are difficult to interpret as they might have been influenced by other factors that were not controlled in the analysis, including patients, epilepsy and seizure characteristics. However, the age-dependent difference in the ictal sympathetic and parasympathetic response [42, 43] may account for potentially distinct manifestations and compensatory mechanisms in the two populations. However, additional studies assessing the occurrence of seizure-related respiratory disfunctions in comparable groups of children and adults are needed, as interestingly, children also have a reduced risk of SUDEP (0.2/1,000) [44] as compared with adults (4/1,000) [45].

Despite occurring in a smaller proportion of seizures, important desaturations are of utmost importance. In fact, patients with severe IH (SpO2<85%) have been demonstrated to be at increased risk of recurrent desaturations [17] and consequently, at potentially higher risk of SUDEP.

In addition to this, severe hypoxemia (SpO2<75%) has also been associated with prolonged ictal central apnea, [12, 34] and severity of respiratory dysfunction in general correlated with the

occurrence of other SUDEP risk factors, including post ictal generalised EEG suppression (PGES) and postictal immobility [14]. Respiratory dysfunctions, including IH and apnea have furthermore been correlated with seizure-related cardiac repolarization abnormalities [46, 47] which are clinically concerning and reflect to those lethal cardiorespiratory dysfunctions involved in the pathophysiology of SUDEP [48].

The duration of a seizure may also have an impact on central respiratory centres and circuits, and our review showed that seizures with desaturation had a longer duration, lasting on average almost 30 seconds more than seizures without desaturation.

Current studies did not provide enough data to compare seizure focus, hemispheric lateralization of the respiratory control, or a presumed higher frequency of IH in patients with right temporal lobe epilepsy [19, 37] or differences in desaturations according to sleep/awake status [31]. In fact, all these variables were only infrequently reported in the studies analysed. Similarly, the effects of AEDs, epilepsy type and gender on the occurrence of IH remain unclear.

Moreover, the meta-regression did not identify methodological variables contributing to the between study heterogeneity, with the exception of the SpO2 desaturation threshold, which alone explained a consistent amount of heterogeneity.

To conclude, our meta-analysis indicated that in epilepsy monitoring units and in a population with refractory epilepsy and long disease duration, IH is a frequent phenomenon, especially in adults and in patients presenting with tonic-clonic seizures.

Nevertheless, the severity of IH appeared independent from the age group and from seizure type and is probably the major clinical concern for its correlation with potentially life-threatening cardiorespiratory alterations and for their association with an increased SUDEP risk.

Although our findings seem to suggest a potential clinical usefulness of a systematic in-hospital and, possibly, out of hospital monitoring of SpO2, several additional factors, including the performance of SpO2 monitors in different settings, the chance of false positive rates and the cost effectiveness, should be carefully evaluated before considering alarms for low oxygen levels as a trigger for early interventions. Moreover, the interventions to be adopted and the effect of such strategies on the risk of cardiorespiratory dysfunctions and SUDEP should be additionally and consequently evaluated.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. MEDLINE search strategy

Appendix S2. Quality Assessment Tool

Figure S1. Cumulative incidence of ictal hypoxemia (IH) by age group

References

[1] Jackson JH. On asphyxia in slight epileptic paroxysms. On the symptomatology of slight epileptic fits supposed to discharge-lesions of uncinate gyrus. Lancet 1899;1:79.

[2] Kennedy JD, Seyal M. Respiratory pathophysiology with seizures and implications for sudden unexpected death in epilepsy. Journal of Clinical Neurophysiology 2015;32:10-13.

[3] Blum AS. Respiratory physiology of seizures. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc. 2009; 26.5:309–15.

[4] Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. J Neurol Neurosurg Psychiatry 1996; 60.3:297–300.

[5] Blum AS, Ives JR, Goldberger AL, Al-Aweel IC, Krishnamurthy KB, Drislane FW, et al. Oxygen desaturations triggered by partial seizures: implications for cardiopulmonary instability in epilepsy. Epilepsia 2000; 41.5:536–41.

[6] Moseley BD, Britton JW, Nelson C, Lee RW, So E. Periictal cerebral tissue hypoxemia: a potential marker of SUDEP risk. Epilepsia 2012; 53.12:e208-211.

[7] Abramo TJ, Wiebe RA, Scott S, Goto CS, McIntire DD. Noninvasive capnometry monitoring for respiratory status during pediatric seizures. Critical care medicine 1997; 25.7: 1242-1246.

[8] Pavlova M, Abdennadher M, Singh K, Katz E, Llewellyn N, Zarowsky M, et al. Advantages of respiratory monitoring during video-EEG evaluation to differentiate epileptic seizures from other events. Epilepsy Behav EB. 2014; 32:142–4.

[9] Goldenholz DM, Kuhn A, Austermuehle A, Bachler M, Mayer C, Wassertheurer S, et al. Long-term monitoring of cardiorespiratory patterns in drug-resistant epilepsy. Epilepsia 2017; 58.1: 77-84.

[10] Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nature Reviews Neurology 2009; 5.9: 492.

[11] Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med 2011; 365:1801–1811.

[12] Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013; 12:966–977.

[13] Moseley BD, Nickels K, Britton J, Wirrell E. How common is ictal hypoxemia and bradycardia in children with partial complex and generalized convulsive seizures? Epilepsia 2010; 51.7: 1219-1224.

[14] Kuo J, Zhao W, Li CS, Kennedy JD, Seyal M. Postictal immobility and generalized EEG suppression are associated with the severity of respiratory dysfunction. Epilepsia 2016; 57:412–417

[15] Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia 2013; 54.2: 377-382.

[16] Seyal M, Hardin KA, Bateman LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. Epilepsia 2012; 53.5:825-31.

[17] Bateman LM, Li CS, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain 2008; 131.12: 3239-3245.

[18] Moseley BD, Wirrell EC, Nickels K, Johnson JN, Ackerman MJ, Britton J. Electrocardiographic and oximetric changes during partial complex and generalized seizures. Epilepsy research 2011; 95.3: 237-245.

[19] Kothare SV, Singh K. Cardiorespiratory abnormalities during epileptic seizures. Sleep medicine 2014; 15.12: 1433-1439.

[20] Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 2009; 151.4: 264-269.

[21] Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions version 5.1.0. (updated March 2011). Chichester: The Cochrane Collaboration; 2011.

[22] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy. A systematic review and meta-analysis of international studies. Neurology 2017; 88:296–303.

[23] Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004; 23:1351–75.

[24] Seyal M, Bateman LM. Ictal apnea linked to contralateral spread of temporal lobe seizures: intracranial EEG recordings in refractory temporal lobe epilepsy. Epilepsia 2009; 50.12: 2557-2562.

[25] Moseley BD, Britton JW. Peri-ictal QTc changes are not associated with hypoxemia. Epilepsy research 2014; 108.5: 982-985.

[26] Moseley BD, So E, Wirrell EC, Nelson C, Lee RW, Mandrekar J, Britton JW. Characteristics of postictal generalized EEG suppression in children. Epilepsy research 2013; 106.1-2: 123-127.

[27] Ives JR, Mainwaring NR, Krishnamurthy KB, Blum AS, Drislane FW, Schachter SC, et al. Technical implementation and clinical findings/results of monitoring oxygen saturation in patients referred for long-term EEG monitoring. Electroencephalography and clinical neurophysiology 1996; 99.5: 432-439.

[28] Lacuey N, Zonjy B, Londono L, Lhatoo SD. Amygdala and hippocampus are symptomatogenic zones for central apneic seizures. Neurology 2017; 10-1212.

[29] Peng W, Danison JL, Seyal M. Postictal generalized EEG suppression and respiratory dysfunction following generalized tonic-clonic seizures in sleep and wakefulness. Epilepsia 2017; 58.8:1409–14.

[30] Hampel KG, Jahanbekam A, Elger CE, Surges R. Seizure-related modulation of systemic arterial blood pressure in focal epilepsy. Epilepsia 2016; 57(10):1709–18.

[31] Latreille V, Abdennadher M, Dworetzky BA, Ramel J, White D, Katz E, et al. Nocturnal seizures are associated with more severe hypoxemia and increased risk of postictal generalized EEG suppression. Epilepsia 2017; 58(9):e127–31.

[32] Tatum WO, Acton EK, Langston ME, Yelvington K, Bowman C, Shih JJ, et al. Multimodality peak Ictal vital signs during video-EEG monitoring. Seizure 2016; 40:15–20.

[33] O'Regan ME, Brown JK. Abnormalities in cardiac and respiratory function observed during seizures in childhood. Dev Med Child Neurol. 2005; 47(1):4–9.

[34] Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. Epilepsia 2010; 51(10):2211–4.

[35] Pavlova M, Singh K, Abdennadher M, Katz ES, Dworetzky BA, White DP, et al. Comparison of cardiorespiratory and EEG abnormalities with seizures in adults and children. Epilepsy Behav EB. 2013; 29(3):537–41.

[36] Singh K, Katz ES, Zarowski M, Loddenkemper T, Llewellyn N, Manganaro S, et al. Cardiopulmonary complications during pediatric seizures: a prelude to understanding SUDEP. Epilepsia 2013; 54(6):1083–91.
[37] Szurhaj W, Troussière AC, Logier R, Derambure P, Tyvaert L, Semah F, et al. Ictal changes in parasympathetic tone: Prediction of postictal oxygen desaturation. Neurology 2015; 85(14):1233–9.
[38] Jaychandran R, Chaitanya G, Satishchandra P, Bharath RD, Thennarasu K, Sinha S. Monitoring peri-ictal changes in heart rate variability, oxygen saturation and blood pressure in epilepsy monitoring unit. Epilepsy Res. 2016; 125:10–8.
[39] Whealy M, Wirrell E, Wong-Kisiel L, Nickels K, Payne ET. Prevalence and Risk Factors of Peri-ictal Autonomic Changes in Children With Temporal Lobe Seizures. Pediatr Neurol. 2017; 67:36–9.
[40] Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. Respiratory changes with seizures in localization-related epilepsy: Analysis of periictal hypercapnia and airflow patterns. Epilepsia 2010; 51(8):1359-64.
[41] Hopkins DA, Holstege G. Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. Experimental Brain Research 1978; 32.4: 529-547.
[42] Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992; 42.9: 1727-1727.
[43] Harnod T, Yang CC, Hsin YL, Shieh KR, Wang PJ, Kuo TB. Heart rate variability in children with refractory generalized epilepsy. Seizure 2008; 17.4: 297-301.
[44] Shankar R, Donner EJ, McLean B, Nashef L, Tomson T. Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. Epileptic Disorders 2017; 19.1: 1-9.
[45] Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrest in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013; 12.10: 966-977.
[46] Kiely DG, Cargill RI, Grove A, Struthers AD, Lipworth BJ. Abnormal myocardial repolarisation in response to hypoxaemia and fenoterol. Thorax 1995; 50:1062–1066.
[47] Roche F, Reynaud C, Pichot V, Duverney D. Effect of acute hypoxia on QT rate dependence and corrected QT interval in healthy subjects. Am J Cardiol 2003; 91:916–919.
[48] Seyal M, Pascual F, Lee CY, Li CS, Bateman LM. Seizure-related cardiac repolarization abnormalities are associated with ictal hypoxemia. Epilepsia 2011; 52(11):2105-11.

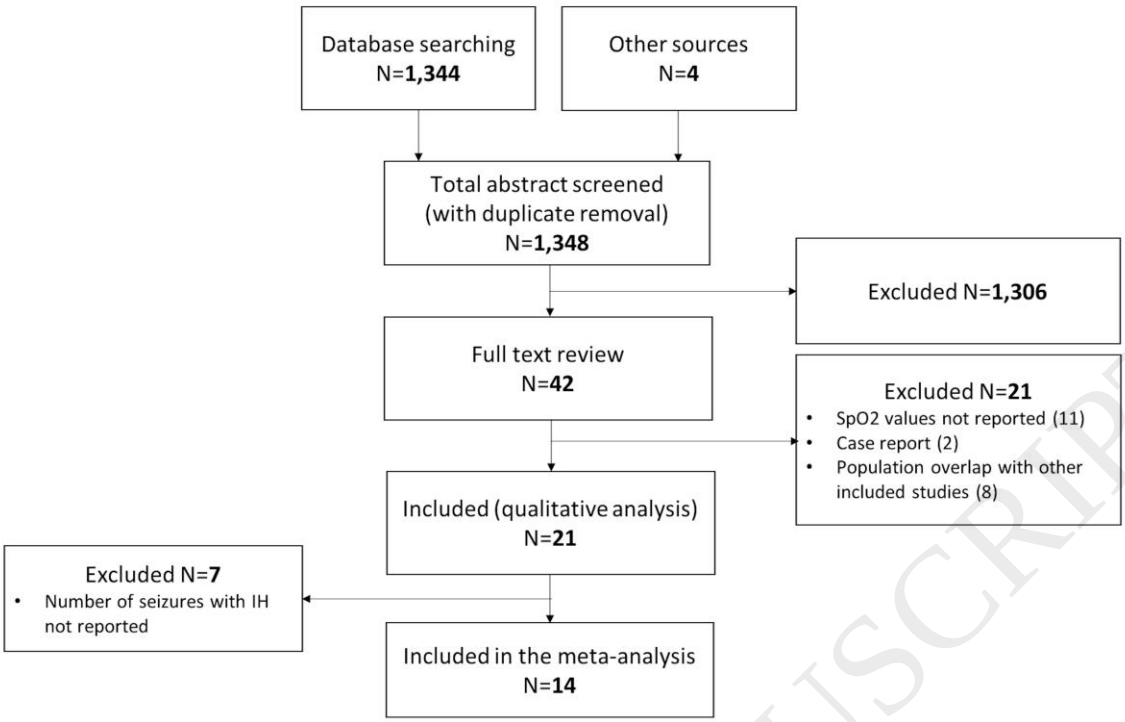


Figure 1. Flowchart of the study selection process. IH: ictal hypoxemia; SpO2: peripheral capillary oxygen saturation

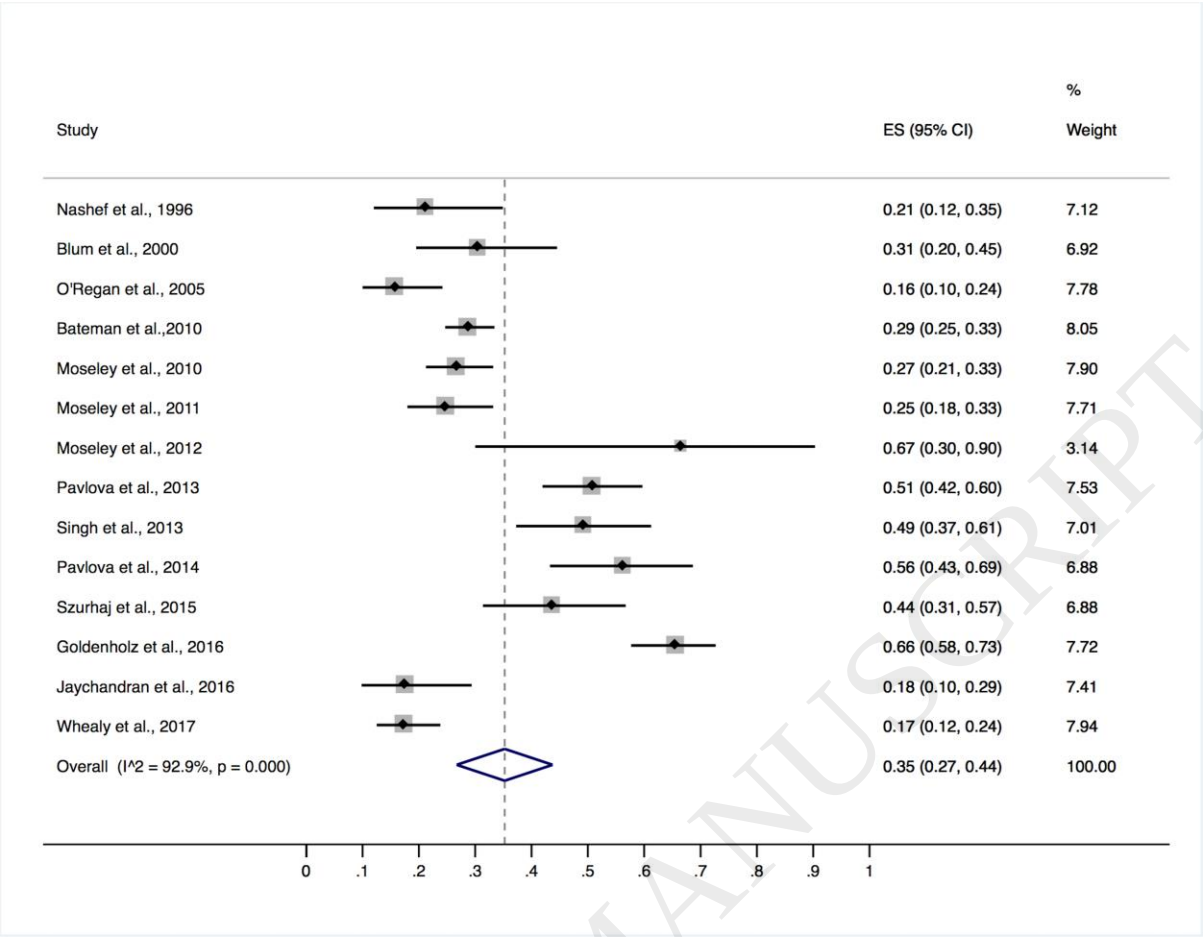
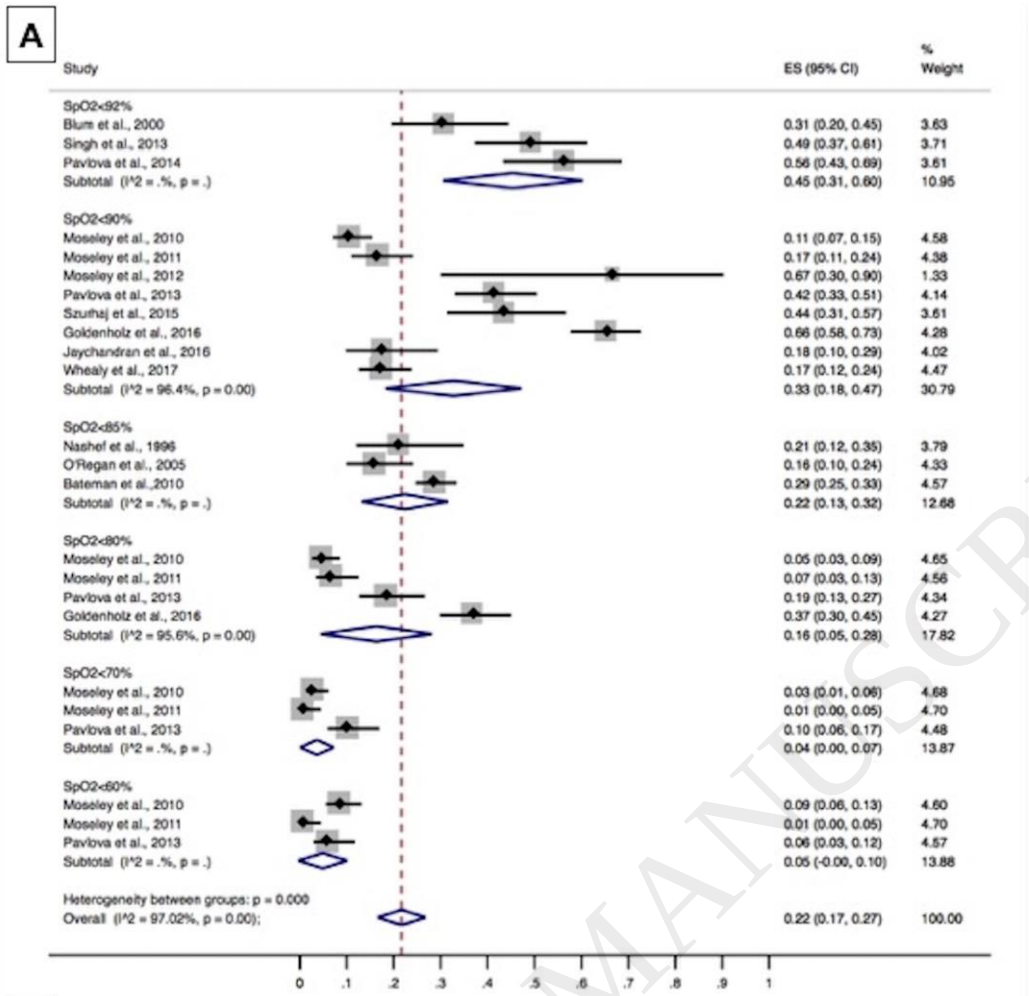


Figure 2. Cumulative incidence of ictal hypoxemia (IH)



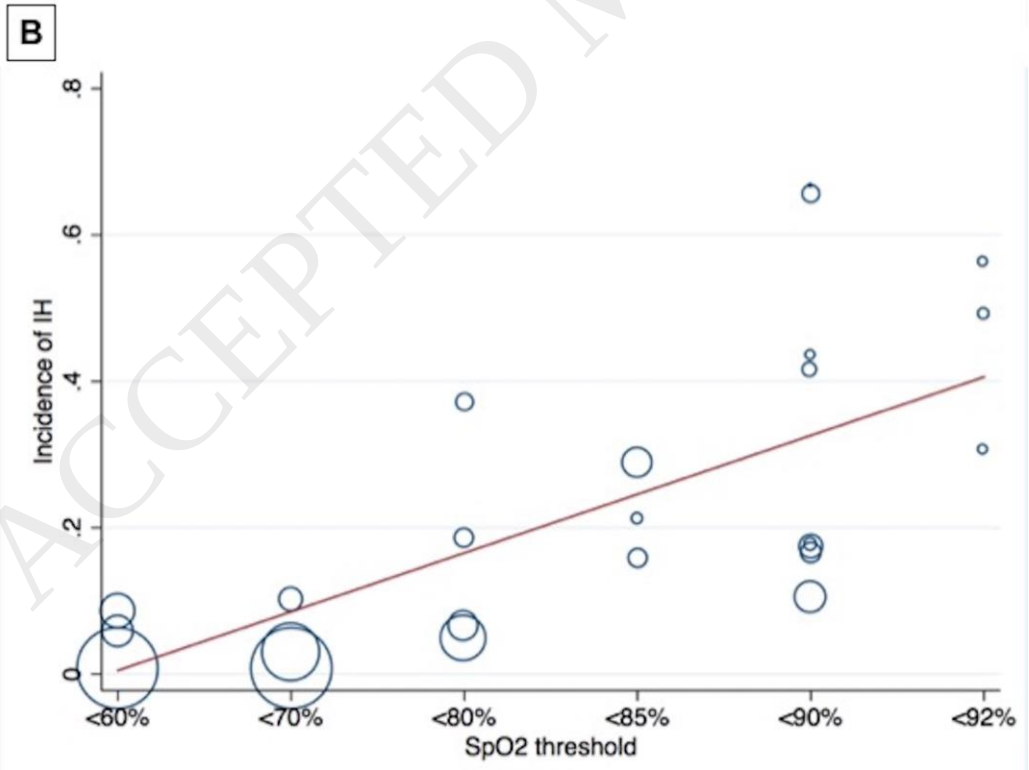


Figure 3. A Cumulative incidence of ictal hypoxemia (IH) by peripheral capillary oxygen saturation (SpO2) threshold; **B** meta-regression bubble plot showing the variation of the incidence of ictal hypoxemia (IH) regressed against the SpO2 threshold (unadjusted p=0.00; adjusted for age group and seizure type p=0.01)

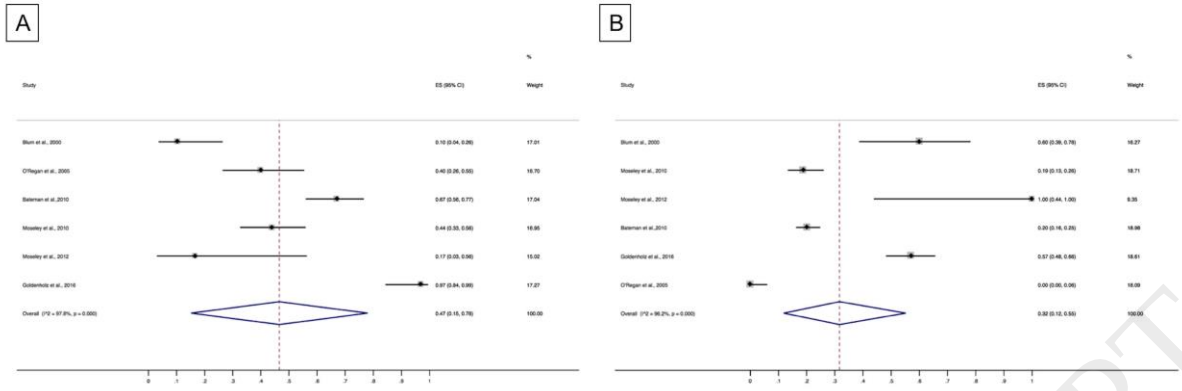


Figure 4. Cumulative incidence of ictal hypoxemia (IH) by seizure type: **A** tonic-clonic seizures, **B** non-tonic-clonic seizures

Tables

Table 1. Characteristics of the included studies (N=21)

Studies	Participants (N)	Age Group	Seizure Type	Total Seizures (N)	Seizures with SpO2 data (N)	SpO2 threshold to define IH	Seizures with IH N, (%)	Duration of IH (seconds)	Seizures with Ictal Apnea N, (%)
Ives et al. 1996[27]	30	not reported	focal and generalized	not reported	not reported	<85%	not reported	not reported	not reported
Nashef et al 1996[4]	17	adult	focal and generalized	47	47	<85%	10 (21.3)	not reported	10 (21.3)
Blum et al. 2000[5]	17	adult	focal	49	49	<92%	15 (30.6)	76.0	not reported
O'Regan et al. 2005[33]	37	children	focal and generalized	101	101	<85%	16 (15.8)	not reported	not reported
Bateman et al. 2010[34]	57	adult	focal	409	409	<85%	118 (28.8)	73.1	not reported
Moseley et al. 2010[13]	47	children	focal and generalized	225	209	<90% <80% <70% <60%	56 (26.8)	not reported	not reported
Moseley et al. 2011[18]	51	adult and children	focal and generalized	218	121	<90% <80% <70% <60%	30 (24.8)	not reported	not reported
Moseley et al. 2012[6]	6	adult	focal and generalized	10	6	<90%	4 (66.7)	not reported	not reported
Pavlova et al. 2013[35]	48	adult and children	focal and generalized	156	118	<90% <80% <70% <60%	60 (50.8)	not reported	not reported
Singh et al. 2013[36]	26	children	focal and generalized	101	63	<92%	31 (49.2)	not reported	29 (46.0)
Pavlova et al. 2014[8]	43	adult	focal and generalized	55	55	<92%	31 (56.4)	not reported	14 (25.4)
Szurhaj et al. 2015[37]	34	adult	focal	55	55	<90%	24 (43.6)	130.0	not reported
Goldenholz et al. 2016[9]	23	adult	focal	193	151	<80%	99 (65.6)	not reported	not reported
Jaychandran et al. 2016[38]	42	adult	focal	57	57	<90%	10 (17.5)	not reported	not reported
Kuo et al. 2016[14]	70	adult	focal and generalized	181	not reported	<90%	not reported	100.6	not reported
Hampel et al. 2016[30]	37	adult	focal	45	not reported	not reported	not reported	not reported	not reported
Tatum et al. 2016[32]	46	adult	focal and generalized	not reported	not reported	<90%	not reported	not reported	not reported
Latreille et al. 2017[31]	20	adult	focal	48	not reported	not reported	not reported	not reported	17 (36.4)
Peng et al. 2017[29]	67	adult	focal and generalized	165	not reported	<90%	not reported	104.5	not reported
Whealy et al. 2017[39]	49	children	focal	172	171	<90%	30 (17.4)	not reported	not reported
Lacuey et al 2018[28]	126	adult	focal and generalized	327	227	<94% <90% ≤75%	not reported	not reported	not reported

IH: ictal hypoxemia; SpO2: peripheral capillary oxygen saturation

Table 2. Meta-regression of incidence of ictal hypoxemia, univariate analysis

Covariates	No. of studies	*p*-value	Heterogeneity ($\tau 2$)	Percent heterogeneity
Study design				
Prospective	3			
Retrospective	11	0.20	0.024	5.68
Age group				
Adults	8			
Children	4	0.35	0.026	-0.37
Adults and Children	2			
Epilepsy type				
Focal and Generalized	7			
Focal	4	0.86	0.028	-9.18
Temporal lobe epilepsy	3			
Drug-resistance				
Refractory	3			
Refractory and not	2	0.54	0.027	-5.25
Unclear	9			
EEG type				
Scalp	11	0.06	0.014	10.54
Scalp and intracranial	2			
Video EEG				
Yes	11			
No	3	0.26	0.025	6.07
Unclear	2			
Severity of ictal hypoxemia				
SpO2<92%	3			
SpO2<90%	8			
SpO2<85%	3	**0.02**	0.021	40.03
SpO2<80%	4			
SpO2<70%	3			
SpO2<60%	3			

SpO2: peripheral capillary oxygen saturation